REACTION OF N-(1-OXIDO-4-PYRIDYL METHYL)-3,5-DIMETHYLBENZAMIDE WITH MALONONITRILE IN ACETIC ANHYDRIDE

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Abstract — Reaction of N-(1-oxido-4-pyridylmethyl)-3,5-dimethylbenzamide with malononitrile in acetic anhydride gives 5-cyano-2-(3,5-dimethylphenyl)-6-(4-pyridyl)-4-(3H)-pyrimidinone.

As part of the research now underway in this laboratory on the chemical behaviour of N-(1-oxido-4-pyridylmethyl)benzamides towards compounds containing active methylene group in acetic anhydride, the reaction of N-(1-oxido-4-pyridylmethyl)-3,5-dimethylbenzamide with malononitrile has been studied. N-(1-oxido-4-pyridylmethyl)-3,5-dimethylbenzamide (0.01 mole) and malononitrile (0.01 mole) were heated at 80°C for 4 h with dimethylformamide (10 ml, DMF) and acetic anhydride (1 ml); the solvent was removed in vacuo, and the residual oil treated with ethyl acetate; a white crystalline solid (16.5%) was obtained. This compound was recrystallized from DMF to give crystals, mp >350°C, which was identified as 5-cyano-2-(3,5-dimethylphenyl)-6-(4-pyridyl)-4-(3H)-pyrimidinone, by analysis of spectral data as shown in experimental.

Fig. 1
As reported for other reactions carried out in the same medium, the first step of the reaction must be the formation of the acetate, followed by that of the di-cyanomethyl derivative. The intermediate thus formed undergoes an internal cyclization by nucleophilic attack of oxygen to one of the cyano groups to give the intermediate oxazine, which gives by ring opening followed by a new cyclization, via nucleophilic addition of an acetate ion. Spontaneous aromatization of in the reaction medium leads to pyrimidinone, according to a mechanism similar to the one proposed by Soto et al. for the formation of 4H-pyrans from α-benzoylcinnamono-nitriles, of Dimroth rearrangement type. (Scheme 1).

Scheme 1

The presence of a variety of dehydrogenating agents seems to have no effect on the reaction yield.
In order to ensure its role as an intermediate, independently prepared $\text{4}^5$ (0.01 mole) was refluxed with malononitrile (0.01 mole) in chloroform (20 ml); $\text{2}$ was actually obtained in higher yield (42%).

**EXPERIMENTAL**

All melting points were determined in open capillary on a Büchi SMP-20 and are uncorrected. IR spectra were performed on a Perkin-Elmer 257. Reported values are the more intense or characteristic peaks. $^1\text{H}-\text{NMR}$ spectra were registered on a Varian MAT 711.

**Reaction of N-oxide $\text{1}$**

1.6 g (0.01 mole) of $\text{N-(1-oxido-4-pyridylmethyl)-3,5-dimethylbenzamide}$, 0.7 g (0.01 mole) of malononitrile, 10 ml of dimethylformamide and 1 ml of acetic anhydride are placed in a round bottomed flask and refluxed at 80°C during 4 h. After standing overnight at room temperature, the solvent is removed in vacuo and the residual oil is treated with ethyl acetate, obtaining 0.5 g (16.5%) of $\text{2-(3,5-dimethylphenyl)-5-cyano-6-(4-pyridyl)-4H-pyrimidinone}$, mp >350°C (DMF). IR (potassium bromide): 3220 (NH), 2230 (CN) and 1665 (CO) cm$^{-1}$; $^1\text{H}-\text{NMR}$ (trifluoroacetic acid): $\delta = 2.502$ (s, 6H, 2CH$_3$), 7.529 (s, 1H, H$_4$-phenyl), 7.978 (s, 2H, H$_2$ and H$_6$-phenyl), 8.897 (d, 2H, H$_3$ and H$_6$-pyridine), 9.200 (d, 2H, H$_2$ and H$_6$-pyridine) ppm; MS: m/e = 302 (100 M$^+$), 274 (80), 259 (15), 171 (75), 143 (20), 132 (25), 116 (20), 105 (15), 77 (10).

Anal. Calcd. for $\text{C}_{18}\text{H}_{14}\text{N}_4\text{O}$: C, 71.51; H, 4.67; N, 18.53. Found: C, 71.22; H, 4.82; N, 18.56.

**Reaction of Acetate $\text{4}$**

3 g (0.01 mole) of $\text{N-(a-acetoxy-4-pyridylmethyl)-3,5-dimethylbenzamide}$, 0.66 g (0.01 mole) of malononitrile and 20 ml of chloroform were refluxed during 8 h. After elimination of the solvent in vacuo, the residual oil is triturated with benzene, giving 1.3 g (42%) of $\text{2}$.

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